77

What is claimed is:

1. A compound of formula (I)

$$R^1$$
 R^{10}
 R^{20}
 R^{10}
 R^{10}

or a pharmaceutically acceptable salt, solvate, or derivative thereof, wherein:

X is a C_{1-5} alkylene chain, wherein said X is optionally substituted by one or more =O, =S, -S(O)_t-, alkyl, or halogen and wherein said C_{1-5} alkylene chain may optionally have 0-3 heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen;

Ring A is a saturated, partially saturated or aromatic 3-7 monocyclic or 8-10 membered bicyclic ring having one ring nitrogen and 0-4 additional heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen;

R¹ is selected from the group consisting of

(a) a saturated, partially saturated, or aromatic 4-7 monocyclic or 8-10 membered bicyclic ring having one ring nitrogen and 0-4 additional heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen, optionally attached through a C₁₋₆ alkylene chain, and optionally substituted by one or more R⁸;

(b)

(c)

(d)

WO 2004/054581 PCT/US2003/039732

Q is carbon, oxygen, or -S(O)t;

w is 1 or 2;

each R² is independently selected from -OR⁰, -C(O)-R⁰, -S(O)₂-R⁰, -C(O)-N(R⁰)₂, -S(O)₂-N(R⁰)₂, -(CH₂)₃-N(R⁰)(-V₀-R⁺), -(CH₂)₃-(-V₀-R⁺), halogen, alkyl optionally substituted by one or more R³, alkenyl optionally substituted by one or more R³, aryl optionally substituted by one or more R³, aryl optionally substituted by one or more R⁶, cycloalkyl optionally substituted by one or more R⁶, cycloalkyl optionally substituted by one or more R⁶, and heterocyclyl optionally substituted by one or more R⁶; and two adjacent R²s on Ring A are optionally taken together to form a fused, saturated, partially saturated or aromatic 5-6 membered ring having 0-3 heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen; or two geminal R²s are optionally taken together to form a spiro, saturated, partially saturated or aromatic 5-6 membered ring having 0-3 heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen, said fused or spiro ring being optionally substituted by one or more R⁶.

a is 0-3;

b is 0 or 1;

V is -C(O)-, -C(O)O-, -S(O)₂-, or -C(O)-N(R°)-:

R⁺ is alkyl, cycloalkyl, aralkyl, aryl, heteroaryl, heteroaralkyl, or heterocyclyl, wherein said R⁺ is optionally substituted by one or more R⁸;

d is 0-1;

m is 0 or 1;

n is 0-5;

each R^3 independently is -H, -N(R^0)₂, -N(R^0)C(O) R^0 , -CN, halogen, -CF₃, alkyl optionally substituted by one or more groups selected from R^7 or -S-aryl optionally substituted by -(CH₂)₁₋₆-N(R^0)SO₂(R^0), alkenyl optionally substituted by one or more groups selected from R^7 or -S-aryl optionally substituted by -(CH₂)₁₋₆-N(R^0)SO₂(R^0), alkynyl optionally substituted by one or more groups selected from R^7 or -S-aryl

optionally substituted by $-(CH_2)_{1-6}$ - $N(R^0)SO_2(R^0)$, cycloalkyl or carbocyclyl optionally substituted by one or more R^6 , aryl optionally substituted by one or more R^6 , heteroaryl optionally substituted by one or more R^6 , or heterocyclyl optionally substituted by one or more R^8 ;

Y is alkyl, alkenyl, alkynyl, $-(CR^4R^5)_p$ -, -C(O)-, -C(O)C(O)-, -C(S)-, -O- $(CH_2)_{0.4}$ -C(O)-, $-(CH_2)_{0.4}$ -C(O)-O-, $-N(R^0)$ -C(O)-, -C(O)-N (R^0) -, $-N(R^0)$ -C(S)-, $-S(O)_{t^-}$, -O-C(=N-CN)-, -O-C(=N-CN)-, -C(=N-CN)-O-, -C(=N-CN)-S-, -C(=N-CN)-, $-N(R^0)$ -C(=N-CN)-, $-N(R^0)$ -C(=N-CN)-, $-N(R^0)$ -C(=N-CN)-, $-N(R^0)$ -C(=N-CN)-, or -C(=N-CN)-; each -CN- independently is H or alkyl optionally substituted by -CN-, alkenyl optionally substituted by -CN-, alkenyl optionally substituted by -CN-, alkynyl optionally substituted by -CN

each R^5 independently is selected from -H, -C(O)-OR⁶, -C(O)-N(R⁰)₂, -S(O)₂-N(R⁰)₂, -S(O)₂-R⁶, aryl optionally substituted by R⁶, or heteroaryl optionally substituted by R⁶:

p is 1-5;

each t independently is 1 or 2;

each R^6 is independently selected from the group consisting of halogen, $-CF_3$, $-OCF_3$, $-OR^0$, $-(CH_2)_{1-6}-OR^0$, $-SR^0$, $-(CH_2)_{1-6}-SR^0$, $-SCF_3$, $-R^0$, methylenedioxy, ethylenedioxy, $-NO_2$, -CN, $-(CH_2)_{1-6}-CN$, $-N(R^0)_2$, $-(CH_2)_{1-6}-N(R^0)_2$, $-NR^0C(O)R^0$, $-NR^0(CN)$, $-NR^0C(O)N(R^0)_2$, $-NR^0C(S)N(R^0)_2$, $-NR^0CO_2R^0$, $-NR^0NR^0C(O)R^0$, $-NR^0NR^0C(O)N(R^0)_2$, $-NR^0NR^0CO_2R^0$, $-C(O)C(O)R^0$, $-C(O)CH_2C(O)R^0$, $-(CH_2)_{0-6}CO_2R^0$, $-O-C(O)R^0$, $-C(O)R^0$, $-C(O)N(R^0)N(R^0)_2$, $-C(O)N(R^0)OR^0$, $-S(O)_1N(R^0)CO_2R^0$, $-OC(O)N(R^0)_2$, $-S(O)_1R^0$, $-S(O)_1N(R^0)C(O)R^0$, $-S(O)_1N(R^0)OR^0$, $-NR^0SO_2N(R^0)_2$, $-NR^0SO_2R^0$, $-C(-S)N(R^0)_2$, $-C(-S)N(R^0)_2$, $-C(-S)N(R^0)_2$, $-C(-S)N(R^0)_2$, $-C(-S)N(R^0)_2$, and $-SO_2N(R^0)_2$ wherein the two $-S^0$ on the same nitrogen are optionally taken together to form a 5-8 membered saturated, partially saturated, or aromatic ring having additional 0-4 heteroatoms selected from oxygen, phosphorus, nitrogen, or sulfur:

each R^7 is independently selected from halogen, $-CF_3$, $-R^0$, $-OR^0$, $-OCF_3$, $-(CH_2)_{1.6}-OR^0$, $-SR^0$, $-SCF_3$, $-(CH_2)_{1.6}-SR^0$, aryl optionally substituted by $-R^6$, methylenedioxy, ethylenedioxy, $-NO_2$, -CN, $-(CH_2)_{1.6}-CN$, $-N(R^0)_2$, $-(CH_2)_{1.6}-N(R^0)_2$, $-NR^0C(O)R^0$, $-NR^0(CN)$, $-NR^0C(O)N(R^0)_2$, $-N(R^0)C(S)N(R^0)_2$, $-NR^0CO_2R^0$, $-NR^0NR^0C(O)R^0$, $-NR^0NR^0C(O)N(R^0)_2$, $-NR^0NR^0CO_2R^0$, $-C(O)C(O)R^0$, $-C(O)C(O)R^0$, $-C(O)C(O)R^0$, $-C(O)C(O)R^0$, $-C(O)C(O)R^0$, $-C(O)C(O)R^0$, $-C(O)N(R^0)_2$,

80

-C(O)N(R⁰)OH, -OC(O)R⁰, -C(O)N(R⁰)SO₂R⁰, -OC(O)N(R⁰)₂, -S(O)_tR⁰, -S(O)_t-OR⁰, -S(O)_tN(R⁰)C(O)R⁰, -S(O)_tN(R⁰)OR⁰, -NR⁰SO₂N(R⁰)₂, -NR⁰SO₂R⁰, -C(=S)N(R⁰)₂, -C(=NH)-N(R⁰)₂, -(CH₂)₁₋₆-C(O)R⁰, -C(=N-OR⁰)-N(R⁰)₂, -O-(CH₂)₀₋₆-SO₂N(R⁰)₂, -(CH₂)₁₋₆-NHC(O)R⁰, and -SO₂N(R⁰)₂ wherein the two R⁰s on the same nitrogen are optionally taken together to form a 5-8 membered saturated, partially saturated, or aromatic ring having additional 0-4 heteroatoms selected from oxygen, phosphorus, nitrogen, or sulfur;

each R^8 independently is selected from the group consisting of R^7 , =0, =S, =N(R^0), and =N(CN);

R⁹ is hydrogen, alkyl optionally substituted by one or more R⁷, alkenyl optionally substituted by one or more R⁷, alkynyl optionally substituted by one or more R⁸, heterocyclyl optionally substituted by one or more R⁸, heterocyclyl optionally substituted by one or more R⁸, or aryl optionally substituted by one or more R⁸; or

-(Y)_m-R³ and R⁹ may combine with the nitrogen atom with which they are attached to form a saturated, partially saturated, or aromatic 5-7 membered monocyclic or 8-10 membered bicyclic ring that optionally contains 1 to 3 additional heteroatoms selected oxygen, phosphorus, sulfur, or nitrogen, wherein said ring may be optionally substituted with one or more R⁸;

R¹⁰ is hydrogen, alkyl optionally substituted by one or more R⁷, alkenyl optionally substituted by one or more R⁷, alkynyl optionally substituted by one or more R⁸, heterocyclyl optionally substituted by one or more R⁸, heterocyclyl optionally substituted by one or more R⁸, or aryl optionally substituted by one or more R⁶;

each R^0 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, carbocyclylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, and heterocyclylalkyl, wherein each member of R^0 except H is optionally substituted by one or more R^* , $-OR^*$, $N(R^*)_2$, =O, =S, halogen, $-CF_3$, $-NO_2$, -CN, $-C(O)R^*$, $-CO_2R^*$, -C(O)-aryl, -C(O)-heteroaryl, aralkyl, $-S(O)_t$ -aryl, $-S(O)_t$ -heteroaryl, $-NR^*SO_2R^*$, $-NR^*C(O)R^*$, $-NR^*C(O)N(R^*)_2$, $-N(R^*)C(S)N(R^*)_2$, $-NR^*CO_2R^*$, $-NR^*NR^*C(O)R^*$, $-NR^*NR^*CO_2R^*$, $-C(O)C(O)R^*$, $-C(O)CH_2C(O)R^*$, $-C(O)N(R^*)_2$, $-C(O)N(R^*)_2$, $-C(O)N(R^*)_2$, and $-SO_2N(R^*)_2$ wherein the two R^*s on the same nitrogen are optionally taken together to form a 5-8 membered saturated, partially saturated or

aromatic ring having additional 0-4 heteroatoms selected from oxygen, phosphorus, nitrogen or sulfur; and

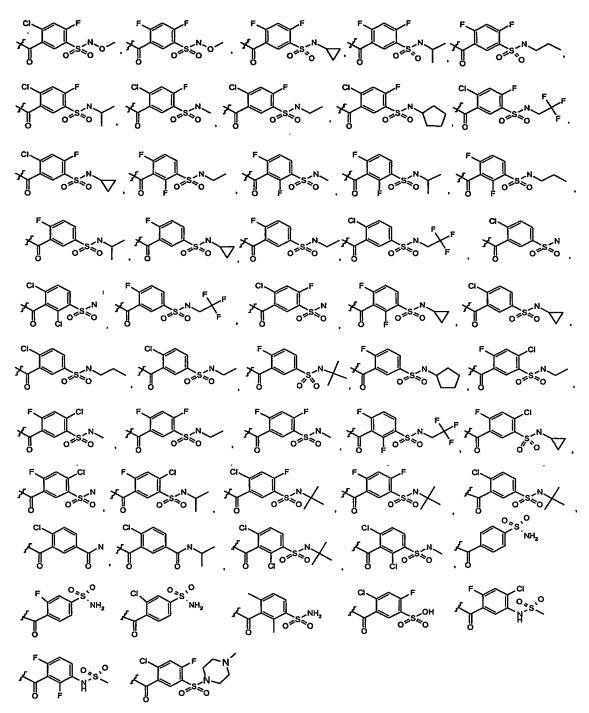
each R* is independently H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or heteroaryl.

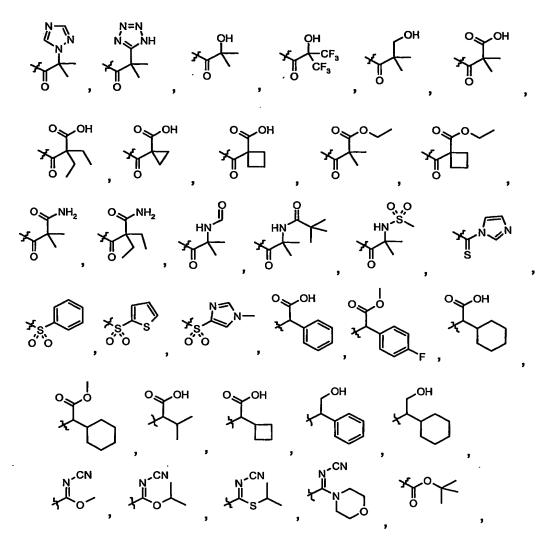
- 2. The compound of claim 1 wherein R¹⁰ is optionally substituted aryl.
- 3. The compound of claim 2 wherein R¹⁰ is optionally substituted phenyl.
- 4. The compound of claim 1 wherein R¹ is

- 5. The compound of claim 4 where R⁹ is alkyl.
- 6. The compound of claim 5 wherein R⁹ is methyl.

7. The compound of claim 4 wherein –(Y)_m-R³ is selected from the group consisting of

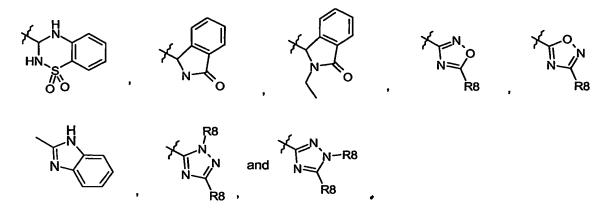
8. The compound of claim 4 wherein $-(Y)_m-R^3$ is selected from the group consisting of





9. The compound of claim 4 wherein $-(Y)_mR^3$ and $-R^9$ combine with the nitrogen atom to which they are attached to form

10. The compound of claim 1 wherein R¹ is selected from



- 11. The compound of claim 1 wherein X is –(CH_2)-, -(CH_2 - CH_2)-, or –(CH_2 - CH_2)-.
- 12. The compound of claim 9 wherein X is optionally substituted by one or more halogen or oxo.
- 13. The compound of claim 9 wherein X optionally has 1-3 heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen.

WO 2004/054581 PCT/US2003/039732

14. The compound of claim 1 wherein the A ring is selected from the group consisting of

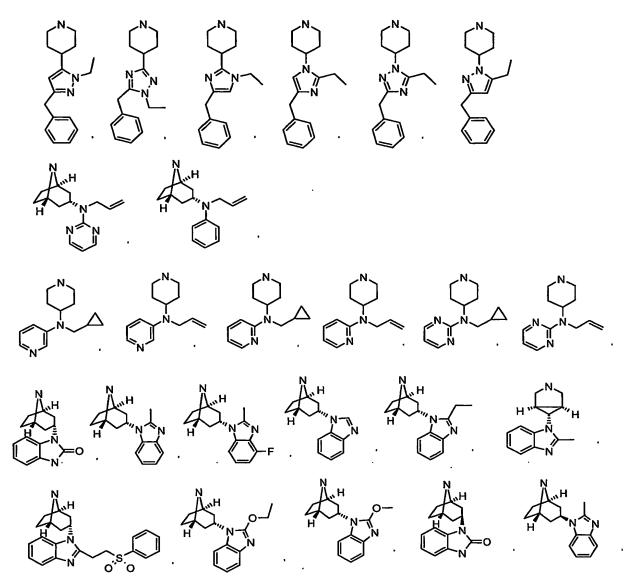
89

15. The compound of claim 12 wherein each R², with an asterisk indicating a point of substitution from Ring A, independently is selected from:

16. The compound of claim 1 wherein ring A, with two geminal R²s, is selected from:

17. The compound of claim 1 wherein the A ring is tropane or piperidine, either optionally substituted with one or more R².

18. The compound of claim 15 wherein the A ring in combination with ${\sf R}^2$ is



- 19. The compound of claim 1 wherein the A ring contains at least one additional nitrogen atom.
- 20. The compound of claim 17 wherein said A ring optionally is N-substituted.
- 21. The compound of claim 18 wherein the A ring is N-substituted with –(CH₂)_a-(V_b-R+).
- 22. The compound of claim 1 wherein the compound of formula (I) is:

wherein X is a C₂-C₃ alkylene chain and R³ and R⁹ are each as defined in claim 1.

- 23. A method of treatment of a viral infection in a mammal comprising administering to said mammal an antiviral effective amount of a compound according to claims 1-20.
- 24. A method according to claim 21 wherein the viral infection is an HIV infection.
- 25. A method of treatment of a bacterial infection in a mammal comprising administering to said mammal an effective amount of a compound according to claims 1-20.
- 26. A method according to claim 23 wherein the bacterium is Yersinia pestis.

- 27. A method of treatment of multiple sclerosis, rheumatoid arthritis, autoimmune diabetes, chronic implant rejection, asthma, rheumatoid arthritis, Crohns Disease, inflammatory bowel disease, chronic inflammatory disease, glomerular disease, nephrotoxic serum nephritis, kidney disease, Alzheimer's Disease, autoimmune encephalomyelitis, arterial thrombosis, allergic rhinitis, arteriosclerosis, Sjogren's syndrome (dermatomyositis), systemic lupus erythematosus, graft rejection, cancers with leukocyte infiltration of the skin or organs, infectious disorders including bubonic and pneumonic plague, human papilloma virus infection, prostate cancer, wound healing, amyotrophic lateral sclerosis and immune mediated disorders in a mammal comprising administering to said mammal a pharmceutically effective amount of a compound according to claims 1-20.
- 28. A compound according to claims 1-20 for use in medical therapy.
- 29. Use of a compound according to claims 1-20 in the manufacture of a medicament for the treatment of a viral infection.
- 30. The use according to claim 27 wherein the viral infection is a HIV infection.
- 31. Use of a compound according to claims 1-20 in the manufacture of a medicament for the treatment of a bacterial infection.
- 32. The use according to claim 29 wherein the bacterium is Yersinia pestis.

WO 2004/054581 PCT/US2003/039732

100

- 33. Use of a compound according to claims 1-20 in the manufacture of a medicament for the treatment of multiple sclerosis, rheumatoid arthritis, autoimmune diabetes, chronic implant rejection, asthma, rheumatoid arthritis, Crohns Disease, inflammatory bowel disease, chronic inflammatory disease, glomerular disease, nephrotoxic serum nephritis, kidney disease, Alzheimer's Disease, autoimmune encephalomyelitis, arterial thrombosis, allergic rhinitis, arteriosclerosis, Sjogren's syndrome (dermatomyositis), systemic lupus erythematosus, graft rejection, cancers with leukocyte infiltration of the skin or organs, infectious disorders including bubonic and pneumonic plague, human papilloma virus infection, prostate cancer, wound healing, amyotrophic lateral sclerosis and immune mediated disorders.
- 34. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claims 1-20 together with a pharmaceutically acceptable carrier.
- 35. The pharmaceutical composition according to claim 32 in the form of a tablet or capsule.
- 36. The pharmaceutical composition according to claim 32 in the form of a liquid.
- 37. A method of treatment of a viral infection in a mammal comprising administering to said mammal a composition comprising a compound according to claims 1-20 and another therapeutic agent.
- 38. The method according to claim 35, wherein said composition comprises another therapeutic agent selected from the group consisting of (1-alpha, 2-beta, 3-alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514, lobucavir], 9-[(2R,3R,4S)-3,4-bis(hydroxymethyl)-2-oxetanosyl]adenine (oxetanocin-G), acyclic nucleosides, acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir, acyclic nucleoside phosphonates, (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC), [[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]phosphinylidene] bis(oxymethylene)-2,2-dimethylpropanoic acid (bis-POM PMEA, adefovir dipivoxil), [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid (tenofovir), (R)-[[2-(6-Amino-9H-purin-9-yl)-1-

1-methylethoxy]methyl]phosphonic acid bis-(isopropoxycarbonyloxymethyl)ester (bis-POC-PMPA), ribonucleotide reductase inhibitors, 2-acetylpyridine 5-[(2chloroanilino)thiocarbonyl) thiocarbonohydrazone and hydroxyurea, nucleoside reverse transcriptase inhibitors, 3'-azido-3'-deoxythymidine (AZT, zidovudine), 2',3'-dideoxycytidine (ddC, zalcitabine), 2',3'-dideoxyadenosine, 2',3'dideoxyinosine (ddl, didanosine), 2',3'-didehydrothymidine (d4T, stavudine), (-)beta-D-2,6-diaminopurine dioxolane (DAPD), 3'-azido-2',3'-dideoxythymidine-5'-H-phosphophonate (phosphonovir), 2'-deoxy-5-iodo-uridine (idoxuridine), (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine), cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), 9-[4hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), ABT-606 (2HM-H2G) ribavirin, protease inhibitors, indinavir, ritonavir, nelfinavir, amprenavir, saquinavir, fosamprenavir, (R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(isoquinolin-5yloxyacetyl)amino-3-methylthiopropanoyl]amino-4-phenylbutanoyl]-5,5- dimethyl-1,3-thiazolidine-4-carboxamide (KNI-272), 4R-(4alpha,5alpha,6beta)]-1,3-bis[(3aminophenyl)methyl]hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2H-1,3diazepin-2-one dimethanesulfonate (mozenavir), 3-[1-[3-[2-(5trifluoromethylpyridinyl)-sulfonylamino]phenyl]propyl]-4- hydroxy-6alphaphenethyl-6beta-propyl-5,6-dihydro-2-pyranone (tipranavir), N'-[2(S)-Hydroxy-3(S)-[N-(methoxycarbonyl)-l-tert-leucylamino]-4- phenylbutyl-N alpha-(methoxycarbonyl)-N'-[4-(2-pyridyl)benzyl]-L- tert-leucylhydrazide (BMS-232632), 3-(2(S)-Hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl)-5.5dimethyl-N-(2-methylbenzyl)thiazolidine-4(R)-carboxamide (AG-1776), N-(2(R)hydroxy-1(S)-indanyl)-2(R)-phenyl-methyl-4(S)-hydroxy-5-(1-(1-(4benzo[b]furanylmethyl)-2(S)-N'-(tert-butylcarboxamido)piperazinyl)pentanamide (MK-944A), interferons, α-interferon, renal excretion inhibitors, probenecid, nucleoside transport inhibitors, dipyridamole, pentoxifylline, N-acetylcysteine (NAC), Procysteine, α -trichosanthin, phosphonoformic acid, immunomodulators, interleukin II, thymosin, granulocyte macrophage colony stimulating factors. erythropoetin, soluble CD₄ and genetically engineered derivatives thereof, nonnucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine (BI-RG-587), alpha-((2-acetyl-5-methylphenyl)amino)-2,6-dichloro-benzeneacetamide (loviride), 1-[3-(isopropylamino)-2-pyridyl]-4-[5-(methanesulfonamido)-1H-indol-2ylcarbonyl]piperazine monomethanesulfonate (delavirdine), (10R, 11S, 12S)-12-hydroxy-6, 6, 10, 11-tetramethyl-4-propyl-11,12-dihydro-2H, 6H, 10H-benzo(1, 2-b:3, 4-b':5, 6-b")tripyran-2-one ((+) calanolide A), (4S)-6-Chloro-4-[1E)-cyclopropylethenyl)-3,4- dihydro-4-(trifluoromethyl)-2(1H)-quinazolinone (DPC-083), (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one (efavirenz, DMP 266), 1-(ethoxymethyl)-5-(1-methylethyl)-6-(phenylmethyl)-2,4(1H,3H)-pyrimidinedione (MKC-442), and 5-(3,5-dichlorophenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbamate (capravirine), glycoprotein 120 antagonists, PRO-2000, PRO-542, 1,4-bis[3-[(2, 4- dichlorophenyl)carbonylamino]-2-oxo-5,8-disodiumsulfanyl]naphthalyl-2, 5-dimethoxyphenyl-1, 4-dihydrazone (FP-21399), cytokine antagonists, reticulose (Product-R), 1,1'-azobis-formamide (ADA), 1,11-(1,4-phenylenebis(methylene))bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride (AMD-3100), integrase inhibitors, and fusion inhibitors.

39. A method of treatment of a viral infection in a mammal comprising administering to said mammal a composition comprising a compound according to claims 1-20 and ritonavir.